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### NOTE

The Next Course in the Medical Aspects of Special Weapons and Radioactive Isotopes for U. S. Naval Reserve Medical and Dental Officers at the U. S. Naval Medical School, National Naval Medical Center, Bethesda, Maryland:

22-26 May 1950

Effects of Delta 5 Pregnenolone in Arthritis: Pregnenolone ( $\Delta^5$ -pregnen- $3\beta$ -ol-20-one, melting point 190 C.) was first obtained synthetically from stigmasterol by oxidation of the C20 side chain and subsequently from cholesterol by the same method. It has been isolated in small amounts from hog testes, but its isolation from human sources has not been reported. Its relation to the physiologically important steroids in chemical structure and in pharmacologic properties has given rise to speculations about its possible role in the human organism as an intermediate substance in the synthesis and metabolism of these steroids. Although chemically it can be regarded as a direct oxidation product of cholesterol, it can, in turn, be transformed into dehydroisoandrosterone by oxidation at C17 into progesterone by oxidation at C3 and into desoxycorticosterone by oxidation at both C3 and C21.

The resting adrenal cortex is rich in cholesterol esters, which are depleted when the experimental animal is subjected to stress or when the adrenal cortex is stimulated by injection of adrenocorticotrophic hormone. There is therefore good evidence that cholesterol is utilized in the synthesis of the steroid hormones, and the pathway of this synthesis may well be through pregnenolone.

Pharmacologically it displays to some extent all the hormonal activities common to the naturally occurring steroids, as shown in animal experiments. It was used extensively by Hoagland and by Pincus to reduce increased ketosteroid excretion which occurs as the result of stress in aviators. Simultaneously with the reduction of the ketosteroid excretion, the psychomotor performance improved. Hoagland postulated that its administration creates an optimum steroid balance, but the mechanism of conversion is obscure. Although these observations were made on essentially healthy persons, pregnenolone also will reduce the excessive ketosteroid excretion of pathologic origin which occurs in virilism in women. It appears to be free from toxic effects in human beings when administered in relatively large doses. Carbohydrate and electrolyte metabolism are unaltered even with prolonged administration, and no effect on renal clearances was observed by Abels and his associates.

The possibility of some disturbance in steroid hormone metabolism in rheumatoid arthritis prompted studies of ketosteroid excretion by the authors and others. Urinary 17-ketosteroid excretion provides an index of adrenocortical activity. The 17-ketosteroids are derived from androgen precursors, two thirds of which in the male and, for practical purposes, all the androgen secreted by the female, are derived from the adrenal cortex. In most chronic debilitating diseases, ketosteroid excretion is low. The authors have confirmed the low excretion rates reported by others in rheumatoid arthritis (additional observations are reported in this paper), although stress of various kinds increases adrenocortical activity and 17-ketosteroid excretion.

How and where ketosteroid precursors are degraded is unknown. Increased adrenocortical activity could account for the observed increase. It might result from a change in the material brought to the adrenal gland or from failure of some mechanism whereby these precursors are converted to substances other than 17-ketosteroids.

Diminished ketosteroid excretion observed in rheumatoid arthritis does not necessarily indicate loss of adrenocortical reserve.

The ability of pregnenolone to reduce 17-ketosteroid excretion and the possibility of readily converting it into other steroids which the individual might utilize to advantage prompted the authors to study the effects of its administration in ankylosing spondylarthritis, the objective being (1) to determine whether pregnenolone would reduce the high rate of ketosteroid excretion which occurs in the disease and (2) to determine what effect the steroid might have on symptoms and course of the disease. A preliminary report of the results in a few cases was presented to the Lane Hospital Medical Society, 15 April 1949. The remarkable clinical improvement observed in these patients prompted trial of pregnenolone in other rheumatic diseases.

Intramuscular injections of pregnenolone have been given to 30 patients. Twelve of these patients, 8 males and 4 females, have typical ankylosing spondylarthritis; 13 patients have rheumatoid arthritis; one has rheumatoid arthritis with spondylarthritis and degenerative joint disease; one, rheumatoid arthritis complicated by glomerulonephritis (this case may be early disseminated lupus), and one, rheumatoid arthritis with psoriasis.

The material used in the investigation was provided by the Schering Corporation. For the initial experiments pregnenolone acetate in sesame oil, 50 mg. per ml., in 10 ml. rubber-capped vials, was supplied. Subsequently, an aqueous suspension of crystalline pregnenolone (100 mg. per ml.) was tried. Use of this material was discontinued because injection of it was difficult. More recently pregnenolone acetate in 80-percent sesame oil and 20-percent benzyl benzoate (50 mg. per ml.) and an aqueous suspension of pregnenolone (50 mg. per ml.) have been used.

All the patients were hospitalized for initial studies, and some were hospitalized for the entire period of investigation. A few were given pregnenolone as ambulatory outpatients. Dosage schedules have been varied from 50 to 300 mg. a day. When pregnenolone acetate was used, 100 mg. was given at a single injection, and when the dosage was increased to 200 mg., 2 injections were given each day. Pregnenolone aqueous suspension in the later experiments has been given in 2 daily injections of 150 mg. each.

Warming of the vials has been necessary to secure solution of the crystals when the acetate in oil was used; otherwise, the oil preparation shows undissolved

crystals. The injection of the cold material occasionally has caused pain in women; such pain did not occur in the males. When the vials were warmed and the material then injected, no pain occurred. When aqueous suspension was given, some of the patients experienced a prickling or stinging sensation at the site of injection for from 5 to 10 minutes after injection.

In most cases, the pattern of response is the same. In spondylarthritis, ketosteroid excretion is reduced in a few days, accompanied with increased mobility of the spine in cases in which fixation was due to spasm, not ankylosis. Pain and spasm were greatly diminished, and in patients with diminished chest expansion it increased. In those patients having rheumatoid arthritis involving joints of the extremities, usually within a week and sometimes within 3 or 4 days there was relief of stiffness and pain, great improvement in muscle strength and loss of fatigue, which was replaced by a feeling of well-being. Appetite was frequently but not invariably improved. In those patients with anemia the blood picture improved rapidly. Reduction in joint swelling, particularly in those cases with large joint effusions, came more slowly. Reduction in sedimentation rates did not parallel clinical improvement but came later.

No evidences of toxicity have been observed from prolonged administration of pregnenolone. There has been no elevation of the fasting blood sugar and no edema. There has been no effect on the menstrual cycle, the duration of menstruation or its character in any of the women who have received it. Pregnenolone is a known stimulant to spermatogenesis; although sperm counts have not been made, none of the men has had diminished potency. One man who had lost sexual potency recovered it while he was under treatment, probably as a result of control of the disease and improvement in general strength.

The euphoria observed by Hemen following large doses of 17-hydroxy-11-dehydrocorticosterone is not seen in patients receiving pregnenolone. However, one patient did become exhilarated and had difficulty sleeping on a daily dosage of 300 mg. of the pregnenolone aqueous suspension.

When use of pregnenolone is discontinued after short term administration, symptoms and signs of active arthritis recur in a few days. One patient who received pregnenolone daily for 37 days and then was given 100 mg. of pregnenolone acetate every 2 days for 2 months continued to show no evidence of arthritis; 5 days after discontinuance of its use pain and joint swelling recurred.

Several patients who have received pregnenolone but are not reported upon in detail in this paper deserve mention. Two men with spondylarthritis who had great clinical improvement from 100 mg. of pregnenolone daily for 3 and 4 weeks respectively were lost by transfer to other hospitals. One man with complete ankylosis of the spine and little residual active disease showed no perceptible change from 50 mg. of pregnenolone acetate daily over a 2-week

period and refused further trial of the steroid. One woman with ankylosing spondylarthritis had a complicating psychosis. She appeared greatly improved in 2 weeks, but evaluation was unsatisfactory because of the psychosis. One woman with psoriasis and rheumatoid arthritis failed to show symptomatic or objective improvement from daily injection of 100 mg. doses of aqueous suspension for 2 weeks, and refused further injections. One 34-year-old man with severe gouty-arthritis was given 200 mg. of pregnenolone acetate for 6 and one-half days without benefit. The same patient was given 100 mg. of pituitary adrenocorticotrophic hormone (ACTH) divided into 6 doses at 6-hour intervals, also without symptomatic or objective improvement, although the ACTH increased excretion of uric acid. One young woman with a diagnosis of disseminated lupus was given 300 mg. of pregnenolone aqueous suspension daily for 2 weeks. The articular symptoms were slightly improved and the swelling was reduced, but she was so greatly emaciated and had so little muscle into which the material could be injected that injections were discontinued. One 54-year-old white woman has had long-continuing active rheumatoid arthritis with much destruction and deformity of joints, and known allergy to many drugs. Her obese buttocks made injections difficult, and because of large, hard, painful nodules which developed from failure in many injections to deposit the oil solution in the muscle, treatment was discontinued.

Although the intramuscular injection of pregnenolone appears to bring about remission in rheumatoid arthritis within a short time, its action in some cases is delayed as long as 3 or 4 weeks. Patients with spondylarthritis with low urinary 17-ketosteroid excretion appear to respond more slowly, and 2 spondylarthritic patients who received what appeared to represent adequate dosage of pregnenolone failed to respond.

The recurrence of symptoms and objective evidence of activity within days after the hormone is discontinued appears to be good evidence that the steroid is responsible for the observed effects. Dosage and form of administration are important considerations. The results of injection of aqueous suspension of crystalline pregnenolone are much less effective than pregnenolone acetate in oil. No obvious effects were observed from daily administration of 50 mg. Many patients responded promptly to 100 mg. whereas others needed 200 mg. daily.

Experience to date indicates that the effective daily dose is 200 mg. A new preparation, which permits use of larger doses, is now being tried to determine whether more rapid control is possible without production of toxic effects. After symptoms have been relieved, reduction in dosage to 100 mg. daily appears sufficient to maintain the benefits; 100 mg. every second day may even be sufficient.

Nothing is known regarding the absorption of pregnenolone, and it appears probable from clinical observation that its administration in oil delays absorption

to furnish a continuous supply of material for conversion to other steroids. Until some knowledge is obtained of its biosynthesis, it seems futile to conjecture how pregnenolone effects remissions in rheumatoid arthritis. Urinary metabolites may give some clue to possible conversions. Studies of these metabolites are now in progress.

Pregnenolone appears to be less rapidly effective than either 17-hydroxy-11-dehydrocorticosterone or the pituitary adrenocorticotrophic hormone (ACTH). Unlike them, it appears to be free of the toxic effects which result from their administration over long periods.

Pregnenolone can be made readily at low expense, an important factor in long-term administration, which appears necessary at the present time. (Arch. Int. Med., March '50, R. Davison et al.)

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Adrenal Function and Blood Electrolytes: Prevailing concepts attribute special physiological significance to the levels of the blood sodium and potassium in relation to steroid hormone function of the adrenal cortex. They are based on the observation that a reduction of sodium and increase of potassium occurs in the blood serum of adrenalectomized animals, and that administration of desoxycorticosterone or its acetate can effect a reversal of that change. It is maintained that this corticoid is a specific hormone of the adrenal cortex whose function is to regulate the balance between those electrolytes in the blood. The probability that loss of something other than any of the adrenal steroids might be responsible for the disturbed electrolyte levels in the blood of adrenalectomized animals has not been given serious attention. In view of the fact that adrenalectomy deprives an animal of function of the adrenal medulla as well as of alleged functions of cortical steroids, the authors undertook this investigation to determine if the physiological secretion of epinephrine might exercise an influence upon the blood sodium and potassium. A possible relationship between epinephrine action and serum potassium is suggested, also, from the results of various pharmacological investigations.

The demonstration by Rogoff and Stewart that sodium chloride is diminished in the blood of completely adrenalectomized dogs included the fact that at least 20 percent of the animals did not develop this change although other changes were present and the animals succumbed to the results of adrenal cortical insufficiency. Bauman and Kurland obtained similar evidence and added the information that an elevation of plasma potassium occurred in adrenalectomized cats. Others have come to consider this as the pathognomonic evidence of adrenal cortical insufficiency although the idea does not have conclusive and unequivocal experimental support. In many instances the increase in potassium can be regarded as a concomitant of hemoconcentration. Significant evidence on this

question is available from the electrical conductivity, specific gravity, and refractometric measurements that were reported by Rogoff and Stewart. The pharmacodynamic effects of adrenalin include an influence upon serum potassium. It seemed possible that the physiological secretion of epinephrine from the adrenal medulla might be concerned with regulation of potassium in the blood, perhaps more so than the influence of the supposed steroid hormone, desoxycorticosterone. This question lends itself to satisfactory quantitative study. From such an investigation it was found that the physiological role of the adrenal glands in relation to blood potassium, hitherto attributed to function of the cortex or one of its steroid components, can be ascribed to a function of epinephrine secretion from the medulla. The level of potassium in the blood serum is diminished by intravenous administration of adrenalin in such amounts and rate of injection as correspond with the physiological rate of epinephrine secretion from the adrenal glands. This effect is obtained in normal dogs and in animals with reduced or suppressed epinephrine secretion. The elevation of blood potassium, which occurs in adrenalectomized dogs, can be corrected by constant intravenous injection of physiological dosage of adrenalin. Higher dosage may effect a rise in serum potassium. A moderate increase in dosage usually induces a preliminary rise followed by a more lasting reduction in the level of potassium. This can also result from too rapid injection of smaller doses. Significant changes in sodium were not constant. The supposed dependence upon the adrenal cortex for maintenance of a physiological equilibrium between sodium and potassium is not supported by the results of the experiments. (Proc. Soc. Exper. Biol. and Med., Feb. '50, J. M. Rogoff et al.)

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Renal Lesions Associated with Chronic Ulcerative Colitis: Although the essential lesions of chronic ulcerative colitis reside in the colon, this disease may cause widespread and important pathologic changes in other parts of the body. This is illustrated by the occurrence of lesions involving the skin, the joints, the vascular system, the eye, and other organs. In addition, marked disturbances in the metabolism of minerals, vitamins and foodstuffs in general are revealed by laboratory studies. These pathologic processes are well recognized and have been described in the literature even though, in many or most instances, the mechanisms involved have not been fully understood. It is evident, however, that the systemic effects of this form of ulcerative colitis are many and varied.

This investigation was undertaken to determine what changes, if any, occur in the kidneys of patients with chronic ulcerative colitis, and to correlate, when possible, such changes with the clinical picture.

It was found that endothelial proliferation (glomerulitis) occurred in 70 percent of a group of 60 cases of chronic ulcerative colitis. The endothelial

proliferation was a slight degree in 36.6 percent, of moderate degree in 21.6 percent, and of high degree in 11.6 percent of the cases. Endothelial proliferation of high degree, with swelling, appeared to cause marked obstruction to the flow of blood in the glomerular capillaries. There was a direct correlation between the degree of endothelial proliferation and the degree of activity of the colitis. The highest degree of endothelial proliferation occurred in the cases of type 1 chronic ulcerative colitis (Bargen's classification). There was no correlation between the degree of endothelial proliferation and the presence of albumin or cellular elements in the urine. It was concluded that chronic ulcerative colitis is probably not an important factor in causing clinical chronic glomerulonephritis. Glomerular function as measured by urea clearance studies was definitely depressed in 3 and questionably depressed in 6 of the 16 patients studied clinically.

Tubular degeneration and necrosis of from slight to moderate degree occurred in 23.3 percent of the 60 cases of chronic ulcerative colitis. Large vacuoles occurred in the tubular epithelium in 5 cases (8.3 percent). The cause and nature of these vacuoles were not determined. Four of the 5 patients with this lesion had terminal oliguria and anuria for a period of from 3 to 6 days before death in spite of adequate therapy with fluids. Deposition of calcium in the tubular epithelium occurred in 15 percent of the cases of chronic ulcerative colitis, as compared with its occurrence in 5.8 percent and 1.7 percent, respectively, in a group of controls with peritonitis and in a group of normal controls.

Acute pyelonephritis occurred in 4 (6.7 percent) of the 60 cases of chronic ulcerative colitis. Chronic pyelonephritis did not occur in any of these cases. The kidneys, in 11 cases in which cultures of urine showed bacteria some time before death, revealed no histologic evidence of pyelonephritis. Six of 22 unselected hospital patients with chronic ulcerative colitis had positive results on culture of the urine in the absence of urinary symptoms.

A renal calculus was present in one of the 60 cases of chronic ulcerative colitis; based upon the experiences of Lindahl and Bargen who concluded that renal calculi occur more frequently after ileostomy in those cases in which the colon is not removed than in those cases in which the colon is removed after the ileostomy, its possible relationship to an ileac stoma made one year before death was considered. Lindahl and Bargen stated their belief that the basis for the formation of the calculi might be urinary infection secondary to the remaining diseased colon.

After ileostomy, there was a tendency to an increase in renal mass. In 45 percent of 20 cases in which ileostomy had been performed, the combined weight of both kidneys was more than 350 Gm. It was concluded that ileostomy in chronic ulcerative colitis has no effect on the incidence or degree of endothelial proliferation or tubular lesions. (Am. J. M. Sc., March '50, E. J. Jensen et al.)

The Significance of Bilirubin Partition in Hepato-Biliary Diseases: The diagnostic significance of the partition of the serum bilirubin into a direct and indirect fraction in jaundice, exclusive of the hemolytic form, is not clearly established. An investigation of this question on a large number of jaundiced patients with verified diagnoses, therefore, appeared indicated. In addition, the recently available, extensive material of liver biopsy specimens offered a chance to study the relation of this partition to liver cell damage. Moreover, because the pathogenesis of jaundice has been associated with changes of the bilirubin fractions, information gained from such studies may serve in re-evaluating this as yet obscure mechanism.

It has long been known that in performing the qualitative diazo reaction of van den Bergh in some instances of jaundice, alcohol had to be added before the characteristic red color was seen (indirect bilirubin or bilirubin A), whereas in others this color appeared without the addition of alcohol (direct bilirubin or bilirubin B). It was assumed that bilirubin which gave the indirect reaction had not reached the liver cells and that that which gave the direct reaction had already passed through them and had regurgitated from the bile capillaries. The chemical or physical differences between the 2 forms of bilirubin have been the subject of much controversy. Apparently they differ mainly in their colloidal state which in turn is responsible for variations in the protein binding.

Many methods have been described for the quantitative determination of both bilirubin fractions in the blood. The application of photoelectric colorimetry to the van den Bergh reaction, particularly as modified by Ducci and Watson, has found widespread acceptance.

After the addition of diazo reagent to serum, the red color may appear promptly and then gradually deepen on standing up to 30 minutes or it may appear only after several minutes. This gave rise to several descriptive terms such as prompt direct, delayed direct, biphasic, and others. Watson demonstrated that there are only 2 components to the reaction, a prompt one and a delayed one, the latter being apparently due to gradual coupling of the indirect bilirubin. Therefore, quantitatively, the direct bilirubin was considered that amount which had reacted in one minute (as determined by the Malloy and Evelyn method). This fraction and the total serum bilirubin are considered the only values of practical significance. Because the reaction is stopped in one minute, Watson prefers the term prompt-reacting bilirubin, which will be employed here.

Using this sensitive photochemical method, it was found that bilirubin is present in normal human serum up to 1.20 mg. per 100 cc., less than 0.2 mg. per 100 cc. of which reacted promptly.

In 279 jaundiced patients, 580 determinations of prompt-reacting and total serum bilirubin were performed according to the method

of Ducci and Watson. Of these, 233 determinations were performed in 114 patients with cirrhosis, 228 in 81 patients with acute hepatitis (viral or toxic), and 123 in 84 patients with extrahepatic biliary obstruction. The diagnoses in these patients had been established by clinical and laboratory observations including a series of hepatic tests and also by the follow-up course, liver biopsy, or autopsy. Only patients with a total serum bilirubin of 2.0 mg. per 100 cc. or more were included. Too few cases of hemolytic jaundice were available for statistical evaluation. In addition, 31 normal adults were used as controls.

Liver biopsy specimens were obtained 153 times in 132 patients, in most cases, by aspiration with a Turkel needle using the right lateral approach through the ninth interspace. In a few cases the liver specimen was obtained at laparotomy. In 34 instances of this series, the biopsy specimen was obtained at a time when the jaundice had subsided.

It was found that the absolute values of the bilirubin fractions and the ratio between them are of no value in differentiating medical and surgical jaundice. However, elevation of the prompt-reacting fraction in subsiding jaundice indicates persistence of the disease process.

The amount of prompt-reacting serum bilirubin was found to depend on the degree of jaundice. As jaundice develops, the prompt-reacting fraction increases more than the indirect. When jaundice is established, both fractions rise fairly parallel. When the bilirubinemia exceeds 40 mg. per 100 cc., the increase of the indirect fraction is greater than that of the prompt-reacting one.

The presence of liver cell damage, as seen in 153 liver biopsy specimens, showed no correlation with the presence or absence of jaundice or the ratio of the prompt to the total bilirubin. A slight but statistically significant correlation was found between the presence of liver cell damage and the absolute values of the prompt-reacting and total bilirubin.

These findings agree with the hypothesis that bilirubin is changed from the indirect to the prompt-reacting form in the Kupffer cells and then transmitted to the liver cells for excretion. Some of the prompt-reacting bilirubin, not taken up by the liver cells, accounts for the small amounts normally present in the blood. In parenchymal jaundice, the liver cells are unable to accept all of the bilirubin and in obstructive jaundice they are unable to excrete it, in either case, resulting in a return of prompt-reacting bilirubin to the bloodstream and the accumulation of bilirubin in the Kupffer cells. This accumulation impairs bilirubin uptake and subsequently the indirect bilirubin increases. (Am. J. M. Sc., March '50, F. Schaffner et al.)

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Significance of the Reference of Anginal Pain to the Right or Left Side of the Body: Anginal pain is felt substernally and often radiates to the sides of the neck and the arms as far as the fingers. This referred pain may occur on both sides, although it is usually much more marked on, or even confined to, the left. Rather infrequently it is restricted to the right. Radiation to the left arm alone occurs about 25 times more often than to the right arm alone, but radiation to both arms is frequent, being about one fourth as common as that to the left arm alone. The more severe the pain or distress in the left arm, the more likely it is to be felt also in the right arm. An attempt is made in this article to attach significance to the side of reference of the pain.

Each of the paired structures in the body is supplied with nerve fibers from the corresponding side of the cord. The same seems to be true of each half of a structure which in the embryo is originally in the midline. The gut and trachea are such structures, and Jackson and Jackson showed that electrode stimulation of the mucosa of the esophagus on one side caused muscular contraction on the same side of the body only. Stimuli in the midline caused contractions on both sides. This shows that one half of the esophagus is connected to the corresponding side of the nervous system only. In a patient recently observed by the writer, bronchoscopy revealed a marked inflammation with vasodilatation strictly confined to the mucosa of the right half of the whole length of the trachea and sharply limited in the sagittal plane. This suggests that the vasodilator nerve fibers from one side of the trachea are derived from that side of the body and nervous system.

On an embryological, phylogenetic, and clinical basis in accordance with the material presented, the author concludes that the right side of the mediastinum, the chambers of the right side of the heart, and the sinoatrial node are right-sided structures and disease affecting these structures may cause right-sided reference of anginal pain. The left side of the mediastinum, left chambers of the heart, pulmonary veins, interatrial septum, and atrioventricular node are left-sided structures. In them disease may cause left-sided anginal pain. The impulses concerned in causing anginal pain arise on the coronary vessels or perhaps in the myocardium and are conducted by unmyelinated fibers passing into the first to fourth (fifth?) dorsal and eighth cervical posterior nerve roots on both sides. In the same nerve roots run fibers supplying the mediastinal structures. If the appropriate left posterior nerve roots are injected with alcohol, anginal pain is abolished on the left side only. It follows that impulses concerned with left-sided pain are transmitted by the fibers passing into the left posterior nerve roots and those with right-sided pain by fibers in the right roots. Because the nerves from the right side of the heart supply the blood vessels of the right chambers and the left nerves those of the left chambers, it follows that right-sided pain means dysfunction of the right chambers and left-sided pain, the left chambers and interatrial septum.

Clinical observations confirm these deductions. In cases of coronary thrombosis or angina occurring in subjects with a heart on the left side of the body the vascular changes and infarction involve chiefly the left ventricle and atrium and sometimes also the right. The pain is usually referred either partially or entirely to the left side and is practically never restricted to the right side. This suggests that greater involvement of the chambers of the left side of the heart is related to the occurrence of greater pain on the left side. In cases of isolated dextrocardia a coronary thrombosis would chiefly involve the right ventricular wall. In a patient with dextrocardia who had angina pectoris, the pain was usually referred entirely to the right, but occasionally spread slightly to the left side. This suggests that pain from disease of the chambers of the right side of the heart is referred by way of the right nerve roots.

The occurrence of angina in a small proportion of patients with mitral stenosis is well known and is usually attributed to accompanying coronary artery disease, but this is not always present. In a patient with mitral stenosis, anginal pain of effort was strictly localized to the right side. A diagnosis of Lutembacher's disease was thought probable. In this patient the extreme dyspnea and cyanosis, enlargement of the pulmonary artery, right ventricle, and atrium, and marked right ventricular preponderance in the electrocardiogram indicate severe pulmonary hypertension with a strain chiefly on the right ventricle. It is significant that the pain was confined to the right side suggesting that it was related to activity of the right ventricle. (Am. Heart J., March '50, R. Wyburn-Mason)

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Complement-Fixing and Neutralizing Antibody Studies on Human Beings Vaccinated Against Rabies: Many workers have reported that neutralizing antibodies develop in the serum of animals and of human beings treated with live or killed rabies vaccines. It also has been shown that complement-fixing antibodies develop to a high titer in rabbits, mice, guinea pigs, and dogs hyperimmunized by repeated injections of living virus. The somewhat meager evidence to date indicates that the 2 antibodies are not identical. Thus Habel found that monkeys developing rabies showed no complement-fixing antibodies although virus neutralizing antibodies were present. Similarly, in experiments carried out in guinea pigs, Nachtigal and Bernkopf, and Nachtigal showed that complement-fixing antibodies reached a maximal titer about a week after the last injection, diminished to one eighth the maximal titer after one month, and disappeared completely within 3 months. On the other hand, neutralizing antibodies reached maximal titers after one month and showed no decrease in titer during the subsequent 3 months of observation.

This communication concerns the results obtained in determining to what extent neutralizing and complement-fixing antibodies are induced in human beings inoculated with the Semple-type, phenol-killed rabies vaccine.

All inoculations were made with the Semple-type, phenol and heat-killed vaccine consisting of 5-percent rabies-infected rabbit brain tissue prepared by the New York City Department of Health. Subcutaneous injections of 2 ml. of vaccine were given each day either for 7 or for 14 consecutive days. The course of treatment was determined on the basis of the criteria set by the New York City Department of Health which stipulates that 14 injections are to be given to those individuals who are bitten by stray animals or by animals that are known to be rabid. The course of 7 injections is given to those who have lesions above the clavicle if the animal is available for examination, and continued through the whole series of 14 injections if such an animal is proven to be rabid. No injections are given to persons with bites inflicted below the clavicle if the animal is known.

Blood samples taken prior to inoculation and at rather frequent intervals after completion of antirabies inoculation were tested from 18 individuals who received 7 injections of vaccine and from 69 individuals who received 14 injections of vaccine. Both neutralizing and complement-fixing antibodies were induced in the 2 groups of inoculated individuals, but in all instances the neutralizing index reached higher levels and persisted longer than did the complement-fixation titer. The highest antibody levels were attained in those patients who received the greater number of vaccine injections. Four individuals had had antirabies vaccine from 6 months to 2 years previously. Three of the 4 still showed an appreciable neutralizing index prior to being reinoculated, and all 4 showed a marked antibody rise or booster effect after the second series of vaccine injections.

The results obtained with the serum specimens in this study are in full accord with those of Habel, Nachtigal, and Bernkopf and Nachtigal who carried out similar tests on a somewhat more limited number of serum specimens from inoculated animals and showed that the virus neutralizing antibodies are quite distinct from the complement-fixing antibodies on the basis of the marked differences noted in their comparative titration end points and time intervals of maintenance. No attempt has been made in this study to determine the nature or properties of the 2 types of antibodies, nor is it intended to imply that there is any correlative relationship between either or both of these antibodies and the degree of immunity attained by the inoculated host. In this connection it is of interest to mention briefly the work of others in this field. Nachtigal reports that 2 independent and different antigens are involved in eliciting neutralizing and complement-fixing antibodies. This was proven by ultracentrifugation experiments with infected mouse-brain suspensions and comparison of the infective and the complement-fixing titers of the sediment and the supernatant fluid.

By use of the ultracentrifuge it was possible to sediment the bulk of the virus without decreasing the original complement-fixing titer of the supernate. The virus-containing sediment did not fix complement at all. Thus the rabies antigen specifically involved in the production of complement-fixing antibodies is not pathogenic, is an entity separate from the infective virus itself, and is apparently of smaller particle size. This is considered to indicate that rabies has a soluble antigen similar to those known to exist in many other virus infections.

Finally it is evident from the literature that there is divergence of opinion concerning whether serum neutralizing antibodies indicate resistance of the host to infection or not. However, the great bulk of evidence indicates that there is no essential or necessary parallelism between the neutralizing antibody titer of the serum and the degree of resistance of the host to infection. Although Kubes and Gallia agree that the serum neutralization test does not give an accurate index of the immunity status of the host, they claim that the brain-tissue neutralization test carried out with brain tissue suspensions of immunized mice gives a true picture of the antirabies immunity of the organism. Although this type of study is worth while and feasible from the laboratory point of view, obviously it could not be carried out with human beings. (Proc. Soc. Exper. Biol. and Med., Feb. '50, I. LeBell et al.)

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Measurements of the Gamma Radiation Doses from Luminous Paint on Instrument Dials in Airplanes: For a large variety of purposes it is necessary to make instruments, handles, footholds, et cetera sufficiently visible in the dark so that, on the one hand, an easy visibility and readability is guaranteed, but, on the other hand, the dark adaptation of the observer is not impaired. There are 3 different types of light-emitting paints for this purpose:

1. Fluorescent paints to which a very minute quantity of a radioactive substance (usually radium) is added as a fluorescence-exciting agent. The fluorescent substance has the power to transform the energy of the hard ionizing rays of the radioactive substance (especially the alpha rays) into visible light. Thus this light is entirely independent of any outer energy supply.
2. Fluorescent paints without exciting substance. These paints do not emit the fluorescent light unless they are irradiated by exciting light. Ultra-violet or violet light is especially efficient for this purpose. This makes it possible to irradiate these paints with a very dark violet or even with an entirely invisible ultraviolet light which does not impair dark adaptation. The disadvantage of these paints is the dependence on an exciting light source, i.e., on power supply. The great advantage is the possibility of regulating the brightness within large limits.

3. Phosphorescent paints. These paints contain substances which are able to stockpile irradiated light energy and to radiate it after the excitation has ceased. Some paints have an afterglow of many hours' duration. The great disadvantages of this type of paint are the dependence on the preceding light charge, the continuously decreasing brightness, and the limitation of the afterglow time.

Although an estimate of the radiation which the pilot in the plane cockpit receives from the radium content in the luminous paint of the instrument panel is well below the tolerance dose, actual measurements were believed worth while. Gamma radiation is the only possible hazard which might be expected. To measure these very small gamma intensities the Minometer of the Victoreen Company (Navy RADIAC SET AN/PDR - 4) was modified in its measuring procedure so that an increase in intensity by about 30 times resulted. The measurements were carried out at a single instrument with an accurately known amount of luminous paint and in the cockpit of a single-engine (F6F) and a 4-engine (PB4Y) plane. The results prove that in all parts of the pilot's body the dosage stays well below the tolerance level. The maximum dosage for the torso amounts to about 4 milliroentgens in 24 hours. For the hand and knees the dosage goes up to 10 milliroentgens in 24 hours, that is 10 percent of the tolerance dose. There is a rapid increase in the doses at very small distances from the instrument panel. Immediately in front of the turn-and-bank indicator the full tolerance dose is reached.

A general curve is derived from the measurements and a graphical method described which permits the precalculation of the spatial distribution of the gamma radiation dosage in the surroundings of any possible instrument grouping. (Proj. NM 001 059.25.01 (formerly NM 001 052), Rep. No. 1, 17 Feb. '50, H. J. Schaefer, School of Aviation Med., NAS, Pensacola, Fla.)

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Complementary Correction of the Defective Coagulation Mechanism of Hemophilic and Thrombocytopenic Blood: In both hemophilic and thrombocytopenic blood the defect of the clotting mechanism reflects a deficiency of active thromboplastin. Evidence has been presented that at least 2 factors are necessary for the activation of thromboplastin, one contained in plasma and the other supplied by the platelets. According to Quick, active thromboplastin is formed through the action of an enzymatic agent liberated by the platelets (thromboplastinogenase) on a plasma precursor (thromboplastinogen). A deficiency of thromboplastin capable of severe impairment of the clotting mechanism may be caused either by (1) lack of thromboplastinogen, (2) lack of thromboplastinogenase, or (3) the presence in the circulation of an agent capable of inhibiting the platelet factor (antithromboplastinogenase). All 3 conditions have been found in definite clinical states: the first in hemophilia,

the second in thrombocytopenic purpura, and the third in some rare types of acquired hemophilia-like disease. Thus, in hemophilia there is adequate thromboplastinogenase (platelet factor), but a lack of thromboplastinogen. In thrombocytopenic blood there is adequate thromboplastinogen, but a lack of thromboplastinogenase. If these assumptions are correct, the addition of hemophilic to thrombocytopenic blood should produce a mixture with a normal clotting mechanism.

The authors have recently been afforded the opportunity of studying simultaneously a patient with classical hemophilia and a 7-year-old girl with a severe thrombocytopenia (9,700 platelets per cm.) of unknown cause presenting, as occasionally found in severe purpura, a somewhat prolonged clotting time (23 minutes in glass tubes). Blood from the 2 patients was mixed in various volumetric proportions. Clotting time, percentage of prothrombin activity left in serum, clot retraction, and accelerator effect of serum were determined in each sample and in the 2 original bloods.

Both hemophilic and thrombocytopenic blood gave normal values for fibrinogen, prothrombin, and labile factor (factor V, Ac globulin of plasma). Neither contained anticoagulant agents. In both bloods there was evidence of lack of thromboplastin activity as indicated by the high values of prothrombin activity of serum and confirmed by the delayed clotting time and very low accelerator effect of serum. When the 2 bloods were mixed in equal volumes, the clotting mechanism became normal. As the proportion of either blood was increased, the prothrombin activity increased and the accelerator effect progressively decreased in serum. However, as little as one part of thrombocytopenic blood in 19 of hemophilic blood reduced the clotting time to normal. Clot retraction, classically defective in thrombocytopenia, became normal when one part of hemophilic blood was mixed with 3 parts of thrombocytopenic blood.

The results presented in this communication support the concept of Brinkhous and Quick that at least 2 factors are necessary for the activation of thromboplastin, one supplied by the plasma and the other by the platelets. The results in this study confirm the finding that the platelet factor is quantitatively and qualitatively normal in hemophilia and suggest that the plasma precursor of thromboplastin is normal in thrombocytopenic blood.

A few other data require comment. Whereas the addition of 1/20 volume of thrombocytopenic blood to hemophilic blood was sufficient to reduce the clotting time to normal it influenced only slightly the consumption of prothrombin. This indicates that the clotting time of whole blood is less accurate than the prothrombin consumption test as a procedure for the study of hemophilia.

The accelerator effect of serum was found to be very low in both hemophilic and thrombocytopenic sera, as previously shown by Alexander and De Vries.

A normal serum accelerator effect could be obtained, however, by allowing thrombocytopenic and hemophilic bloods to clot in the presence of thromboplastin. In the authors' experiments, the accelerator effect of serum appeared to be indirectly proportional to the prothrombin activity of serum. (Proc. Soc. Exper. Biol. and Med., Feb. '50, M. Stefanini and W. H. Crosby)

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Effects of Desoxycorticosterone Acetate (DOCA) and Methylene Blue in Rheumatoid Arthritis: It is important to find out whether the interaction of desoxycorticosterone acetate (DOCA) and ascorbic acid leads to the formation of a third substance, and if so, what this substance is. There are 3 chief possible ways in which DOCA and ascorbic acid may react with each other: (1) formation of a complex compound, (2) reduction of DOCA, and (3) oxidation of DOCA. It seems most probable that ascorbic acid oxidizes DOCA. The hormones isolated from the adrenal cortex may theoretically be regarded as oxidation products of cholesterol. Following the administration of adrenocorticotrophic hormone (ACTH), the amount of ascorbic acid and of cholesterol in the adrenal cortex is reduced. Apparently ascorbic acid is in some way physiologically active in the synthesis of adrenal cortical hormones.

One way to test whether ascorbic acid oxidizes DOCA when injected in this combined treatment is to try to obtain the same clinical effect by substituting another oxidizing agent for ascorbic acid. The author used methylene blue.

The patients were given intramuscular DOCA, 5 mg. and immediately afterwards intravenous methylene blue, 8 ml. of a 5-percent solution. Controls were given either methylene blue alone, DOCA alone, ascorbic acid alone, or DOCA and ascorbic acid according to the method of Lewin and Wassen. The results were judged by the range of mobility in each joint and by the patients' ability to walk, close their hands, put their hands on their back, or to the nape of their neck, etc. The only side effect of methylene blue is a bitter taste just after injection. The patients show a profound cyanosis, which disappears in a few minutes. In some cases the treatment began with DOCA and methylene blue and in others with DOCA and ascorbic acid.

The method has been tried on 8 patients so far. Of these, 6 had typical rheumatoid arthritis, one incipient rheumatoid spondylitis, and one probably acute gouty arthritis. In all the cases the same rapid and pronounced improvement was obtained after combined treatment with DOCA and methylene blue as well as after combined treatment with DOCA and ascorbic acid. The rapidity of action was the same with each method as was also the objective improvement. The effect after treatment with DOCA and ascorbic acid usually lasted longer than that after treatment with DOCA and methylene blue, but the amount of

methylene blue injected has only about a fifth of the oxidizing effect of the amount of ascorbic acid injected. The subjective improvement was equal with the 2 methods. The patients felt the same after the different injections, their joints were more flexible, the pains disappeared, and mobility increased. The injection of DOCA alone never had any effect. In most cases the author observed an insignificant but undoubted objective improvement after treatment with ascorbic acid alone or methylene blue alone.

If the same substance is formed when DOCA and methylene blue are injected as when DOCA and ascorbic acid are injected, as the results suggest, this substance is an oxidation product of DOCA, methylene blue being an oxidizing agent.

The slight beneficial effect from the injection of methylene blue alone or ascorbic acid alone can be explained by the oxidation of steroids present in the body into active substances.

The fact that the full beneficial effect is reached only if DOCA is given together with methylene blue or ascorbic acid proves that the active substance formed by the combined treatment originates chiefly from the DOCA.

These experiments suggest that the physiological role of ascorbic acid in the suprarenal glands is that of oxidizing the steroids present into various active adrenal hormones. (Lancet, 25 Feb. '50, Leif Hallberg, assistant physician, County Hospital, Ornskoldsvik, Sweden)

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#### Results of Spinal Pyramidotomy for Treatment in the Parkinsonian

Syndrome: Surgery should be considered for the relief of tremor in patients with parkinsonian syndrome in whom satisfactory results have not been obtained from the use of medical measures. It has been clearly shown by several surgeons that relief of tremor is possible following various procedures which destroy the pyramidal tract to a greater or less degree, but it remains to be seen which of the operative methods yields the most satisfactory results in the long run.

Aside from such practical considerations, many questions of great theoretic importance also are involved, for each of the surgical operations which has been proposed constitutes an interesting physiologic experiment.

The purpose of the present paper is to analyze a series of 22 cases of the parkinsonian syndrome which could be followed for a period of 12 months or more after operation. The total number of patients operated on is now over twice that number, but some cannot be reached and it is too early to draw dependable conclusions from the others. Most of the patients whose cases are included here were examined by one or the other of the authors in person, but in a few cases data furnished by other physicians were accepted. Preoperative

and postoperative motion picture records were taken and used in the analysis whenever possible. Particular attention was paid to the influence of the operation on the tremor and on other manifestations of parkinsonism considered separately; also to the impairment of strength and motility at various intervals following operation. The general course of the disease process was recorded and, in particular, any increase in rigidity or spread of tremor to previously unaffected portions of the body. In cases with bilateral symptoms, any alteration in the condition of the side contralateral to the operation was given particular attention.

The technic of spinal pyramidotomy has already been described, and no important changes have been made in the operative procedure. A hemilaminectomy at the second cervical vertebra is to be preferred, and the lamina should be removed as far laterally as possible. Exposure is facilitated if the incision in the dura is curved, with the base of the flap at the level of the posterior roots, or even farther laterally. The landmarks are clear, and there is seldom difficulty in obtaining a field free of small pial vessels. If necessary, hemostasis may be assured by a touch of a cautery, heated only to a point sufficient to cause it to adhere to connective tissue. This operation may easily be combined with Puussepp's operation, of section of posterior columns. Such a combined procedure was carried out in 5 cases, 4 of which are included in the present series. Its effect on rigidity was negligible. Surprisingly, disturbances of sensation were extremely slight. The authors hope to report more fully on them elsewhere.

All the operations reported here were unilateral; the use of a combination of spinal pyramidotomy with homolateral cortical operation at a later stage and of bilateral spinal operations will be described in a later paper.

By the use of the technic described, the exposure is so good and the landmarks are so clear that there can be little question that the procedure divides the lateral pyramidal tract and little else. A specimen was presented in the original paper to demonstrate this fact, but the present series does not permit any further proof of it, as there have been no deaths.

The age at onset of the first symptoms varied with the underlying disease process. A history suggestive of encephalitis was obtained in 6 cases, and in these the symptoms began in the second or third decade of life. In the majority of cases, no etiologic factors were apparent and the disorder was classified as idiopathic. In this group, there was a gradual development of tremor and rigidity beginning in the fourth or fifth decade. In 2 cases, the sudden onset at the ages of 65 and 68 respectively and the presence of pronounced vascular changes led the authors to assume that the disease was arteriosclerotic in origin. For 2 patients, whose first symptoms began at the ages of 22 and 23 respectively, no history of encephalitis or other probable etiologic disorder could be elicited, nor was there any evidence of a corneal ring or disturbance of function of the liver. These 2 cases are provisionally considered as belonging to the juvenile idiopathic group. The characteristic syndrome of regular alternating parkinsonian tremor and rigidity was seen in all cases. The term rigidity is used to characterize all akinetic phenomena, the loss of spontaneity, the slowness and

inefficiency of active movements, the typical waxy resistance to passive movements and the loss of associated and synergistic innervation. The regularity of the alternating tremor and the characteristic synchronous firing of motor units in the affected muscles were studied in slow motion pictures and by electromyography.

In 5 cases, only one side was involved, usually to a crippling extent, with the other side substantially normal. In 4 other cases, the tremor was unilateral but both sides were affected by rigidity. In 13 cases, tremor and rigidity were present bilaterally, but in 11 of these the symptoms were much severer on one side than on the other.

All patients had undergone intensive treatment with various atropine and belladonna preparations. The interval between the onset of the first symptoms and the operation was never less than one year; in 13 cases it was less than 2 years; in 7, between 26 and 43 months, and in 2 cases, 50 months or more.

All patients were severely handicapped in the use of the affected extremities, particularly by the intensity of the alternating tremor. Relief from this distressing symptom was urgently requested by each of them, even though the possibility of a loss of motor power was carefully explained to them. The majority of patients applying for surgical relief of their parkinsonian state were advised against having an operation, usually on the grounds that their chief disability consisted of rigidity rather than of tremor.

This series of 22 cases could be followed for a considerably longer period after operation than was possible in the series of 6 cases reported when the operation of section of the lateral pyramidal tract was first suggested in 1940. The larger series and longer duration of observation appear to place the indications for operation on a firmer basis. In the first publication it was stated that from the practical therapeutic point of view, it appeared justifiable to conclude that operative treatment offers considerable hope of relief from severe unilateral tremor. In this group of 22 patients with severe, disabling parkinsonian tremor, two thirds showed a satisfactory improvement which lasted for at least a year (one third of the patients experienced complete relief; in an additional third of the patients the tremor was markedly reduced, and only one third had results that can be considered failures).

It cannot be too often repeated that these generally favorable results relate to improvement of the tremor only. Neither section of the pyramidal tract nor any of the cortical extirpations which have been recommended are to be considered a treatment of parkinsonism; they are treatments only of tremor. The rigidity is seldom affected and the progress of the underlying disease is not checked. A complete and distinct understanding should always be reached with the patient and his family on this score; but in properly selected cases the prospects for improvement of function and increase of comfort may easily outweigh the disadvantages of the operation. If severe rigidity is present, improvement of function can scarcely be expected, but the patient may be rendered much more comfortable. The likelihood that the patient's condition will be made substantially worse in the long run

as a result of this operation is extremely small. In this respect, it has a great advantage over the cortical operations, which often lead to disastrous results and at best usually produced a more serious disturbance of function than does the operation under discussion.

The danger to muscular power and control from this operation (and also from those at a cortical level) must be considered by both the surgeon and the patient. Both should realize that there is a risk of about 1 in 3 that the strength of the extremities involved will be substantially decreased even after the immediate postoperative period. If the tremor is in itself incapacitating, the exchange is usually for the better; but in other cases the possibility of further disability must be weighed against the probability of relief from tremor.

There appears to be no clear correlation between the age of the patient, the type of the disease or the postoperative relief from tremor and the incidence of paralysis after operation. There were 13 cases in this series in which there was no evidence of impairment of strength at the end of the period of observation. In 8 of these cases, there was satisfactory relief of tremor; in 5, little or no relief. Of the 9 cases in which there was considerable reduction of strength and control of the affected extremities, there was a satisfactory relief of tremor in 7 and unsatisfactory relief in 2.

A comparable study of the results of the cortical operation (resection of the premotor area) in parkinsonism has not as yet been published. The available observations give definite evidence that the cortical approach also may yield good results in the improvement of tremor. However, epileptic manifestations seem to be a quite frequent manifestation after cortical resection. Although complete analyses of results of the cortical operation are not available, the authors have personally seen and learned of many cases, especially those in which substantial amounts of cortex have been resected, in which severe and permanent paralyses and aphasiae have occurred. The cortical operations appear, therefore, to be more dangerous in every way than the spinal pyramidotomies.

Although the final comparison between the cortical and spinal operation has to be postponed, 2 considerations are clear. The spinal pyramidotomy affects upper and lower extremities of one side. Cortical resection may be limited to one arm area. In solitary tremor of one upper extremity the cortical operation might, therefore, be preferred in order to prevent reduction of power in the lower extremity as a possible after-effect of the operation. Further, the cortical approach offers the opportunity of ascertaining approximately what result can be expected before the extirpation is actually carried out. (Arch. Neurol. and Psychiat., March '50, T. J. Putnam and E. Herz)

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Benzene Hexachloride-Resistant Houseflies: In October 1948 the junior author and the International Health Division of The Rockefeller Foundation initiated a housefly-control campaign in the Egyptian village of Quarafil. One

of the measures used was the application of benzene hexachloride dusts containing 2.4 percent of the gamma isomer to all places suspected of being breeding areas. The treatment was renewed whenever the previous one showed signs of losing its effectiveness. During the first 10 months fresh applications were made approximately once a month. A high degree of reduction in the number of houseflies was maintained throughout most of this period. Because an adequate control could no longer be maintained in August, September, and October of 1949, the intervals between dustings were gradually shortened until applications were being made weekly. The development of a strain of benzene hexachloride-resistant houseflies was considered.

To find out if such had occurred, a series of laboratory tests was run by the senior author during November and December 1949 against houseflies (Musca domestica vicina Macq) collected from 9 different sources including 6 villages in addition to Quarafil, a slaughter house in one of the suburbs of Cairo, and a laboratory reared colony. Quarafil was the only place in which large scale housefly control measures were being used.

In one series all 9 colonies were exposed for 30 minutes. At least 99 percent mortality was obtained within 24 hours against the 8 colonies that had not been subjected to control measures. In contrast, less than half of the Quarafil strain was killed indicating that this strain actually had acquired considerable resistance to benzene hexachloride.

Another series was run with the Quarafil, slaughter house, and laboratory strains to obtain more precise information on the degree of resistance that had developed. In these tests the exposure period was varied between 5 and 120 minutes to obtain a range of mortalities that would permit a comparison of the contact times required to kill similar percentages of the different colonies. Altogether, 1,796 male and 1,511 female flies were used in these tests. It was readily apparent from the results that the Quarafil strain was much more difficult to kill than the slaughter house or laboratory strains. An exposure that was sufficient to cause 100-percent mortality of those from the 2 untreated sources killed only 15 percent of the males and 12 percent of the females from the resistant stock. The 5-minute exposure killed from 65 to 67 percent of the slaughter house and laboratory females but a 2-hour exposure was required to kill a comparable percentage of those from the benzene hexachloride-treated village, indicating the latter flies were about 24 times as resistant to this insecticide as the other 2 strains. The degree of resistance acquired by the males appeared to be even greater.

With female flies the greatest differences were observed in the 30-minute tests in which the mortality obtained in individual tests was always at least 67 percent lower for the resistant flies than the corresponding exposure of slaughter house or laboratory flies. Similarly the kill of males from the untreated sources always exceeded that of the Quarafil stock by at least 78 percent in the 5-minute tests. There were no reversals in any of the comparisons.

Entomologists had hoped that benzene hexachloride would be one of the residual-type insecticides that could be used satisfactorily in situations in which houseflies have developed resistance to DDT. The results obtained in Quarafil indicate that any benefit derived from a change to this insecticide might be only temporary. (Proj. NM 005 050.15.01, 15 Feb. '50, J. B. Gahan and J. M. Weir, Naval Medical Research Unit No. 3, Cairo, Egypt)

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A Resilient Interdental Splint for Use in Boxing: To replace the presently used stock rubber mouthpiece, used in boxing, a flexible vinyl resin mouthpiece, made from dental impressions and models of the individual wearers, has been developed by Doctors J. V. Niiranen and H. J. Towle at the U. S. Naval Dental School, National Naval Medical Center, Bethesda, Maryland.

The principal deficiencies of the standard stock rubber mouthpiece are imperfect fit with cushioning unevenly distributed over a relatively few points of contact, poor retention, jaw separation of from 13 to 15 mm., and discomfort to the wearer. This new splint has the advantages of positive retention with comfort, complete and evenly distributed cushioning of all surfaces, only 3 mm. of jaw separation with resultant greater muscle comfort, and no interference with breathing.

These new splints are soon to be tested in boxing matches in the Navy. There is evidence to believe that through their use there will be a diminished occurrence of fractured mandibles and other injuries to the dental arch and teeth.

The new splint is being considered for use in football and also in bruxism (grinding of teeth during sleep).

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Navy's Health at All-Time High for Second Consecutive Year: The health of personnel of the U. S. Navy reached an all-time high for the second consecutive year in 1949, according to statistics of the Bureau of Medicine and Surgery, which has kept complete medical department records since 1850. New low rates for incidence of diseases, injuries, deaths, and days lost from illness were established.

In 1949 the annual incidence rate for disease and injuries of all kinds among naval personnel dropped to 376.0 per 1,000 strength - a 15-percent drop from the previous low of 442.8, set in 1948. Except for the last 5 years, during 4 of which the incidence rate hung around 490 per 1,000, this rate has rarely dropped below 500.0.

Fewer common colds and a 33-percent reduction in the incidence rate for venereal diseases contributed largely to the 1949 disease and injury record.

The fact that the average person in the Navy lost less than a week's time, 6.7 days, from duty because of illness in 1949 constituted another new health record. The average number of days lost from illness varied from 8 to 15 per person during the years from 1900 through 1948.

The death rate among naval personnel, which has maintained a downward trend since 1900, was 1.8 per 1,000 in 1949. This new low rate compares with the previous low of 1.9 in 1940 and 2.0 in 1948. The death rate in 1900 was 8.9 per 1,000.

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Training Program in Hospital Administration for Officers of the Medical Service Corps, Regular Navy: The Navy Medical News Letter, Volume 13, Number 10, dated 20 May 1949, announced the establishment of a program whereby a limited number of officers of the Medical Corps and the Medical Service Corps of the regular Navy, might receive an academic year of instruction in hospital administration. This program will be continued during the academic year of 1950-51 for officers of the Medical Service Corps (Administrative and Supply) only.

The use of the following civilian institutions is contemplated for this training:

Columbia University, New York, New York  
Johns Hopkins University, Baltimore, Maryland  
Northwestern University, Chicago, Illinois  
University of California, Berkeley, California  
University of Chicago, Chicago, Illinois  
University of Minnesota, Minneapolis, Minnesota  
Washington University, St. Louis, Missouri  
Yale University, New Haven, Connecticut

Those who complete this training and satisfactorily fulfill all requirements of the university concerned will be awarded a master's degree in hospital administration. The institutions listed require that applicants for admission have at least a bachelor's degree, except that in the instance of the University of Minnesota an applicant not meeting the minimum academic requirements may be enrolled as a special student. Such a student receives the same instruction in all respects as those fully eligible but is not awarded the master's degree upon completion of the prescribed training. The university instruction will be followed by a calendar year of supervised administrative assistantship (administrative internship) in a naval hospital.

Requests are desired from interested officers of the Medical Service Corps (Administrative and Supply) in all ranks. Each request must contain an agreement not to resign during the course of instruction and to serve 3 years in the U. S. Navy upon completion of the period of training. To receive consideration, requests must reach BuMed prior to 1 July 1950 and may be made by dispatch if the time element involved requires such action. Requests submitted by dispatch must be confirmed by a following letter. (Professional Div., BuMed)

Inactive Naval Reserve Medical Officers Needed to Volunteer for Active Duty and Temporary Assignment with the U. S. Air Force: The Surgeon General of the U. S. Air Force has requested that the Bureau of Medicine and Surgery circularize the inactive Naval Reserve medical officers for volunteers for temporary assignment to duty with the U. S. Air Force.

Volunteers for active duty will be acceptable for tours of duty of one or 2 years to fill the present and anticipated vacancies within the continental United States and if desired, in overseas theaters. Requests for this active duty with the Air Force are desired from medical officers in the grades of lieutenant (junior grade) through lieutenant commander, and who are not more than 40 years of age. Reserve medical officers who have been designated by the Navy as flight surgeons or aviation medical examiners will be entitled to flight pay if they meet the required physical qualifications.

Naval Reserve medical officers volunteering for duty with the Air Force will wear the Navy uniform and be carried on the rolls of the Navy as an officer on active duty. They will receive full pay and allowances of their rank with the additional \$100 per month authorized for medical officers on active duty. Living quarters for officers and their families are available at the majority of continental Air Force activities.

The Bureau of Medicine and Surgery will furnish application forms and particular information on available U. S. Air Force duty stations to interested Reserve medical officers upon receipt of written request. Such request should be directed to the Bureau of Medicine and Surgery (Code 3), via the commandant of the naval district in which the applying medical officer lives. (Reserve Div., BuMed)

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Correction in News Letter Note on BuMed Circular Letter 50-23: The manufacturer of the binders for the 1949 revision of the Manual of the Medical Department has guaranteed to place in first-class working order, at no cost, any binders that show evidence of defect up to 12 December 1959 (not 1950 as stated in the note on BuMed Circular Letter 50-23 beginning on page 29 of the 24 March issue).

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BUMED CIRCULAR LETTER 50-27

20 March 1950

From: Chief, Bureau of Medicine and Surgery  
To: All Stations under Management Control of the Bureau of Medicine and Surgery

Subj: NAVMED-732, Request for Work; Cancellation of

This letter states that in the future, Medical Department activities shall submit NavSandA Form 140, Request for Performance of Work, in lieu of subject form, to the Public Works Officer in accordance with instructions contained in Bureau of Supplies and Accounts Manual.

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BUMED CIRCULAR LETTER 50-28

22 March 1950

From: Chief, Bureau of Medicine and Surgery  
To: All Medical Department Activities and Facilities Ashore  
Subj: Nomenclature and Definitions Pertaining to Fixed Medical Treatment Facilities

Encl: (1) Office of the Secretary of Defense memorandum of 27 Jan 1950 to the Secretaries of the Army, the Navy, and the Air Force

1. Enclosure (1) is forwarded for information. BuMed circular letters implementing subject definitions will be issued at an early date. H. L. Pugh

Enclosure (1)

MEMORANDUM FOR THE SECRETARY OF THE ARMY  
THE SECRETARY OF THE NAVY  
THE SECRETARY OF THE AIR FORCE

Subject: Nomenclature and Definitions Pertaining to Fixed Medical Treatment Facilities

1. In order to effect more uniformity in the nomenclature and definitions used in the Department of Defense with respect to fixed medical treatment facilities, it is the policy of the Department of Defense to use the following nomenclature and definitions with reference to the "capacities" and the "bed status" of such facilities:

A. With respect to "capacities" of fixed medical treatment facilities:

(1) Mobilization Bed Capacity is space for patients' beds and is measured in terms of the number of beds which can be set up in wards or rooms designed for patients' beds, spacing beds six feet between centers (approximately 72 square feet per bed). Former ward space which has been disposed of or has been structurally altered to serve another purpose is not included in computing bed capacities. Space for beds used only in connection with examination or brief treatment periods, such as that in examining rooms or in the physiotherapy department, is not included in this figure. Nursery space is not included in the bed capacity but is accounted for separately in terms of the number of bassinets it accommodates.

(2) Normal Bed Capacity, or capacity for normal peacetime use, is space for patients' beds and is measured in terms of the number of beds which can be set up in wards or rooms designed for patients' beds, spacing beds eight feet between centers (approximately 100 square feet per bed). Former ward space which has been structurally altered to serve another purpose is not included in computing bed capacities. Space for beds used only in connection with examination or brief treatment periods, such as that in examining rooms or in the physiotherapy department, is not included in this figure. Nursery space is not included in the bed capacity but is accounted for separately in terms of the number of bassinets it accommodates.

B. With respect to the use being made of the above "bed capacities" of fixed medical treatment facilities (i.e., as to the availability of beds set up and as to the status of the remaining spaces for beds):

(1) Operating Beds are those medical treatment facility beds which are currently set up and in all respects ready for the care of patients and which the facility is staffed and equipped to operate. Bassinets for the use of newborn infants in the nursery are not included in the count of operating beds, but are accounted for separately.

(a) Occupied Beds is the number of operating beds in a medical treatment facility which are currently assigned to patients. It does not include any beds for patients who are on leave or absent without leave.

(b) Operating Beds Available is the number of operating beds in a medical treatment facility which are not currently assigned to patients.

(2) Inactive Beds are those medical treatment facility bed spaces with beds, not necessarily set up, for which equipment and fixtures are on hand and installed, but for which operating staff is not provided. Inactive beds may be converted to operating beds within a day or two after the necessary staff is made available.

(3) Latent Reserve Beds are those medical treatment facility bed spaces for which are lacking not only the required staff but also some or all of the equipment and fixtures necessary to convert them to operating beds. Maintenance repairs may be required to effect this conversion. The time required to convert latent reserve beds to operating beds will vary and may be prolonged.

It is intended that a fixed medical treatment facility operating with beds set up on eight-foot centers (approximately 100 sq. ft. per bed) will also count inactive beds and latent reserve beds on this basis. Thus, when no space is being counted by mobilization capacity criteria, the sum of the operating beds, inactive beds and latent reserve beds is equal to the normal bed capacity. A fixed medical treatment facility currently authorized to set up operating beds on six-foot centers (approximately 72 square feet per bed) will count inactive beds and

latent reserve beds on the basis of six-foot centers (by mobilization capacity criteria) and also on the basis of eight-foot centers (by normal capacity criteria).

2. The above seven (7) terms for standard use throughout the Department of Defense will supplant the larger number of nonstandard terms of this nature heretofore variously used. The use of terms having indefinite or not uniformly understood meanings, such as maximum capacity, constructed capacity, emergency capacity, authorized capacity, beds assembled and beds vacant, will thus be obviated.

3. It is requested that you take the necessary action in your departments to implement the above Department of Defense policy at the earliest possible date, so that reports for periods beginning on or after 1 April 1950 will be in conformity with the above nomenclature and definitions.

Approved: 20 Mar 1950  
Dan A. Kimball  
Under Secretary of the Navy

/s/ Leven C. Allen  
Major General, U.S.A.  
Executive Secretary

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